Hepatitis B

Viral hepatitis is a term commonly used for several clinically similar yet etiologically and epidemiologically distinct diseases. Hepatitis A (formerly called infectious hepatitis) and hepatitis B (formerly called serum hepatitis) have been recognized as separate entities since the early 1940s and can be diagnosed with specific serologic tests. Delta hepatitis is an infection dependent on the hepatitis B virus (HBV). It may occur as a coinfection with acute HBV infection or as superinfection of an HBV carrier.

Epidemic jaundice was described by Hippocrates in the 5th century B.C. The first recorded cases of serum hepatitis, hepatitis B, are thought to be those that followed the administration of smallpox vaccine containing human lymph to shipyard workers in Germany in l883. In the early and middle parts of this century, serum hepatitis was repeatedly observed following the use of contaminated needles and syringes. The role of blood as a vehicle for virus transmission was further emphasized in 1943, when Beeson described jaundice among seven recipients of blood transfusions. Australia antigen, later called hepatitis B surface antigen (HBsAg), was first described in 1965, and the Dane Particle (complete hepatitis B virion) was identified in 1970. Identification of serologic markers for HBV infection followed, which helped clarify the natural history of the disease. Ultimately, HBsAg was prepared in quantity and now comprises the immunogen in highly effective vaccines for the prevention of HBV infection.

HEPATITIS B VIRUS

HBV is a small, double-shelled virus in the family Hepadnaviridae. Other Hepadnaviridae include duck hepatitis virus, ground squirrel hepatitis virus, and woodchuck hepatitis virus. The virus has a small circular DNA genome that is partially double-stranded. HBV contains numerous antigenic components, including HBsAg, hepatitis B core antigen (HBcAg), and hepatitis B e antigen (HBeAg). Humans are the only known host for HBV, although some nonhuman primates can be infected under laboratory conditions. HBV is relatively resilient and, in some instances, has been shown to remain infectious on environmental surfaces for at least a month at room temperature.

HBV is the most common cause of chronic viremia known, with an estimated 200 to 300 million chronic carriers worldwide. HBV infection is an established cause of acute and chronic hepatitis and cirrhosis. It is the cause of up to 80% of hepatocellular carcinomas, and is second only to tobacco among known human carcinogens. More than 250,000 persons die worldwide each year of hepatitis B-associated acute and chronic liver disease.

Several well-defined antigen-antibody systems are associated with HBV infection. **HBsAg**, formerly called Australia antigen or hepatitis-associated antigen, is an antigenic determinant found on the surface of the virus. It also makes up subviral 22-nm spherical and tubular particles. HBsAg can be identified in serum 30 to 60 days after exposure to HBV and persists for variable periods. HBsAg is not infectious. Only the complete virus (Dane particle) is infectious. However, when HBsAg is present in the blood, complete virus is also present, and the

person may transmit the virus. During replication, HBV produces HBsAg in great excess.

HBcAg is the nucleocapsid protein core of HBV. HBcAg is not detectable in serum by conventional techniques, but can be detected in liver tissue in persons with acute or chronic HBV infection. **HBeAg**, a soluble protein, is also contained in the core of HBV. HBeAg is detected in the serum of persons with high virus titers and indicates high infectivity. **Antibody to HBsAg (Anti-HBs)** develops during convalescence after acute HBV infection or following hepatitis B vaccination. The presence of HBsAb antibody indicates immunity to HBV. **Antibody to HBcAg (Anti-HBc)** indicates infection with HBV at an undefined time in the past. IgM class antibody to HBcAg (IgM anti-HBc) indicates recent infection with HBV. **Antibody to HBeAg (Anti-HBe)** becomes detectable when HBeAg is lost and is associated with low infectivity of serum.

CLINICAL FEATURES

The clinical course of acute hepatitis B is indistinguishable from that of other types of acute viral hepatitis. The **incubation period** ranges from 6 weeks to 6 months (average, 120 days). Clinical signs and symptoms occur more often in adults than in infants or children, who usually have an asymptomatic acute course. However, approximately 50% of adults who have acute infections are asymptomatic.

The **preicteric, or prodromal, phase** from initial symptoms to onset of jaundice usually lasts from 3 to l0 days. It is nonspecific and is characterized by insidious onset of malaise, anorexia, nausea, vomiting, right upper quadrant abdominal pain, fever, headache, myalgias, skin rashes, arthralgias and arthritis, and dark urine, beginning 1 to 2 days before the onset of jaundice. The **icteric phase** is variable, but usually lasts from l to 3 weeks, characterized by jaundice, light or gray stools, hepatic tenderness and hepatomegaly (splenomegaly is less common). During **convalescence**, malaise and fatigue may persist for weeks or months, while jaundice, anorexia, and other symptoms disappear.

Most acute HBV infections in adults result in complete recovery with elimination of HBsAg from the blood and the production of anti-HBs creating immunity from future infection.

COMPLICATIONS

While most acute HBV infections in adults result in complete recovery, **fulminant hepatitis** occurs in about 1% to 2% of persons, with mortality rates of 63% to 93%. About 200 to 300 Americans die of fulminant disease each year. Although the consequences of acute HBV infection can be severe, most of the serious complications associated with HBV infection are due to chronic infection.

Chronic HBV Infection

Approximately 10% of all acute HBV infections progress to chronic infection, with the risk of chronic HBV infection decreasing with age. As many as 90% of infants who acquire HBV infection from their mothers at birth become carriers. Of children who become infected with HBV between 1 year and 5 years of age, 30% to 50% become carriers. By adulthood, the risk of becoming a carrier is 6% to 10%.

Persons with chronic infection are often asymptomatic and may not be aware that they are infected, yet are capable of infecting others. Chronic infection is responsibile for most HBV-related morbidity and mortality, including **chronic hepatitis, cirrhosis, liver failure, and hepatocellular carcinoma**. Chronic active hepatitis develops in over 25% of carriers, and often results in cirrhosis. An estimated 3,000 to 4,000 persons die of hepatitis B-related cirrhosis each year in the United States. Persons with chronic HBV infection are at 12 to 300 times higher risk of hepatocellular carcinoma than noncarriers. An estimated 1,000 to 1,500 die each year in the United States of hepatitis B-related liver cancer.

LABORATORY DIAGNOSIS

Diagnosis is based on clinical, laboratory, and epidemiologic findings. HBV infection cannot be differentiated on the basis of clinical symptoms alone, and **definitive diagnosis depends on the results of serologic testing**. Serologic markers of HBV infection vary depending on whether the infection is acute or chronic.

HBsAg is the most commonly used test for diagnosing acute HBV infections or detecting carriers. HBsAg can be detected as early as 1 or 2 weeks and as late as 11 or 12 weeks after exposure to HBV when sensitive assays are used. The presence of HBsAg indicates that a person is infectious, regardless of whether the infection is acute or chronic.

Anti-HBc (core antibody) develops in all HBV infections, appears shortly after HBsAg in acute disease, and indicates HBV infection at some undefined time in the past. Anti-HBc only occurs after HBV infection, and does not develop in persons whose immunity to HBV is from vaccine. Anti-HBc generally persists for life and is not a serologic marker for acute infection.

IgM anti-HBc appears in persons with acute disease about the time of illness onset and indicates recent infection with HBV. IgM anti-HBc is generally detectable 4 to 6 months after onset of illness and is the best serologic marker of acute HBV infection. A negative test for IgM-anti-HBc together with a positive test for HBsAg in a single blood sample identifies a chronic HBV infection.

HBeAg is a useful marker associated strongly with the number of infective HBV particles in the serum and a higher risk of infectivity.

Anti-HBs (surface antibody) is a protective, neutralizing antibody. The presence of anti-HBs following acute HBV infection generally indicates recovery and immunity from reinfection. Anti-HBs can also be acquired as an immune response to hepatitis B vaccine or passively transferred by administration of HBIG. Using radioimmunoassay (RIA), a minimum of 10 sample ratio units should be used to designate immunity. Using enzyme immunoassay (EIA), the manufacturer's recommended positive should be considered an appropriate measure of immunity. The level of anti-HBs may also be expressed in milli-International Units/mL (mIU/mL). Ten mIU/mL is considered to indicate a protective level of immunity.

Interpretation of Hepatitis B Serologic Tests

Tests	Results	Interpretation
HBsAg anti-HBc anti-HBs	Negative Negative Negative	Susceptible
HBsAg anti-HBc anti-HBs	Negative Negative Positive with ≥10mIU/mL*	Immune due to vaccination
HBsAg anti-HBc anti-HBs	Negative Positive Positive	Immune due to natural infection
HBsAg anti-HBc IgM anti-HBc anti-HBs	Positive Positive Positive Negative	Acutely infected
HBsAg anti-HBc IgM anti-HBc anti-HBs	Positive Positive Negative Negative	Chronically infected
HBsAg anti-HBc anti-HBs	Negative Positive Negative	Four interpretations possible†

*Postvaccination testing, when it is recommended, should be performed 1-2 months following dose #3.

† 1. May be recovering from acute HBV infection.
2. May be distantly immune and the test is not sensitive enough to detect a very low level of anti-HBs in serum.
3. May be susceptible with a false positive anti-HBc.
4. May be chronically infected and have an undetectable level of HBsAg present in the serum.

MEDICAL MANAGEMENT

There is no specific therapy for acute HBV infection. Interferon is the most effective treatment for chronic HBV infection and is successful in 25% to 50% of cases.

Persons with acute HBV infections and carriers should prevent their blood and other potentially infective body fluids from contacting other persons. They should not donate blood, or share

toothbrushes or razors with household members.

In the hospital setting, patients with HBV infection should be managed with standard precautions.

EPIDEMIOLOGY

Reservoir

Although other primates may be infected experimentally, HBV infection affects only humans. No animal or insect hosts or vectors are known to exist.

Transmission

The virus is transmitted by **parenteral or mucosal exposure to HBsAg-positive body fluids** from persons who are carriers or have acute HBV infection. The highest concentrations of virus are in blood and serous fluids; lower titers are found in other fluids, such as saliva and semen. Saliva can be a vehicle of transmission through bites; however, other types of exposure to saliva, including kissing, are unlikely modes of transmission. There appears to be no transmission of HBV via tears, sweat, urine, stool, or droplet nuclei.

In the United States, the most important route of transmission is by **sexual contact**, either heterosexual or homosexual, with an infected person. Fecal-oral transmission **does not** appear to occur. However, transmission among homosexual men occurs possibly via contamination from asymptomatic rectal mucosal lesions.

Direct percutaneous inoculation of HBV by needles during injection drug use is an important mode of transmission. Transmission of HBV may also occur by other percutaneous exposure, including tattooing, ear piercing, and acupuncture, as well as needle-sticks or other injuries from sharp instruments sustained by medical personnel. These exposures account for only a small proportion of reported cases in the United States. Breaks in the skin without overt needle puncture, such as fresh cutaneous scratches, abrasions, burns, or other lesions, may also serve as routes for entry.

Contamination of mucosal surfaces with infective serum or plasma may occur in mouth pipetting, eye splashes, or other direct contact with mucous membranes of the eyes or mouth, such as hand-to-mouth or hand-to-eye when contaminated with infective blood or serum. Transfer of infective material to skin lesions or mucous membranes via inanimate environmental surfaces may occur by touching surfaces of various types of hospital equipment. Contamination of mucosal surfaces with infective secretions other than serum or plasma could occur with contact involving semen.

Perinatal transmission from mother to infant at birth is very efficient. If the mother is positive for both HBsAg and HBeAg, 70%-90% of infants will become infected in the absence of

postexposure prophylaxis. The risk of perinatal transmission is about 20% if the mother is positive only for HBsAg. Up to 90% of these infected infants will become HBV carriers. An estimated 15%-25% of these carriers will ultimately die of liver failure secondary to chronic active hepatitis, cirrhosis, or primary hepatocellular carcinoma.

The frequency of infection and patterns of transmission vary in different parts of the world. Approximately 45% of the global population live in areas with a high prevalence of chronic HBV infection (>8% of the population is HBsAg-positive); 43% in areas with a moderate prevalence (2% to 7% of the population is HBsAg-positive); and 12% in areas with a low prevalence (<2% of the population is HBsAg-positive).

In China, Southeast Asia, most of Africa, most Pacific Islands, parts of the Middle East, and the Amazon Basin, 8% to l5% of the population carry the virus. The lifetime risk of HBV infection is >60%, and most infections are acquired at birth or during early childhood, when the risk of developing chronic infections is greatest. In these areas, because most infections are asymptomatic, very little acute disease related to HBV occurs, but rates of chronic liver disease and liver cancer in adults are very high. In the United States, Western Europe, and Australia, HBV infection is a disease of low endemicity. Infection occurs primarily during adulthood, and only 0.1% to 0.5% of the population are chronic carriers. Lifetime risk of HBV infection is <20% in low prevalence areas.

Communicability

Persons with either acute or chronic HBV infection should be considered infectious any time that HBsAg is present in the blood. When symptoms are present in persons with acute HBV infection, HBsAg can be found in the blood and body fluids of infected persons for 1 to 2 months before and after the onset of symptoms.

SECULAR TRENDS IN THE UNITED STATEs

Hepatitis has been reportable in the United States for many years. Hepatitis B became reportable as a distinct entity during the 1970s, after serologic tests to differentiate different types of hepatitis became widely available.

The incidence of reported hepatitis B peaked in the mid-1980s, with about 26,000 cases reported each year. Reported cases have declined since that time, and fell below 10,000 cases for the first time in 1996. In 1999, a provisional total of 6,495 cases were reported. The decline in cases during the 1980s and early 1990s is generally attributed to reduction of transmission among homosexual men and injection drug users as a result of HIV prevention.

Reported cases of HBV infection represent only a fraction of cases that actually occur. In 1999 a total of 7,694 cases of acute hepatitis B were reported to CDC. Based on these reports, CDC estimates that 21,500 acute cases of hepatitis B resulted from an estimated 79,000 new infections. An estimated 1-1.25 million persons in the United States are chronically infected with HBV, and an additional 5,000-8,000 persons become chronically infected each year.

More than 80% of acute HBV infections occur among adults. Adolescents account for approximately 8% of infections, and children and perinatal transmission account for approximately 4% each. Perinatal transmission accounts for a disproportionate 24% of chronic infections.

The most common risk factor for HBV infection in the United States is sexual contact, either heterosexual (41%), or homosexual (9%). Injection drug use accounts for 15% of cases, 2% of cases occur by household contact with a chronic carrier, and health care workers account for 1% of cases. Approximately 30% of all persons with HBV infection have no known risk factor for infection.

Although HBV infection is uncommon among adults in the general population (the lifetime risk of infection is <20%), it is highly prevalent in certain groups. Risk for infection varies with occupation, lifestyle, or environment (see next table). Generally, the highest risk for HBV infection is associated with lifestyles, occupations, or environments in which contact with blood from infected persons is frequent. In addition, the prevalence of HBV markers for acute or chronic infection increases with increasing number of years of high risk behavior. For instance, an estimated 40% of injection drug users become infected with HBV after 1 year of drug use, while over 80% are infected after 10 years.

Prevalence of Hepatitis B in Various Population Groups

Population Group		Prevalence of Serologic Markers of HBV Infection	
		HBsAg (%)	All Markers (%)
High Risk	Immigrants/refugees from areas of high HBV endemicity.	13	70-85
	Clients in institutions for the developmentally disabled.	10-20	35-80
	Users of illcit parenteral drugs.	7	60-80
	Homosexually active men.	6	35-80
	Patients of hemodialysis units.	3-10	20-80
	Household contacts of HBV carriers.	3-6	30-60
Intermediate	Prisoners (male).	1-8	10-80
	Health care workers – frequent blood contact.	1-2	15-30
	Staff of institutions for the mentally retarded.	1	10-25
	Heterosexuals with multiple partners.	0.5	5-20
Low	Health care workers – no or infrequent blood contact.	0.3	3-10
	Healthy adults (first-time volunteer blood donors).	0.3	3-5

HEPATITIS B PREVENTION STRATEGIES

Hepatitis B vaccines have been available in the United States since 1981. However, the impact of vaccine on HBV disease has been less than optimal, and the incidence of reported hepatitis B cases is now only slightly less than as it was before the vaccine was licensed.

The apparent lack of impact from the vaccine can be attributed to several factors. From 1981 until 1991, vaccination was targeted to people in groups at high risk of HBV infection. A large proportion of persons with HBV infection (25% to 30%) deny any risk factors for the disease. These persons would not be identified by a targeted risk factor screening approach.

The three major risk groups (heterosexuals with contact with infected persons or multiple partners, injection drug users, and men who have sex with men), are not reached effectively by targeted programs. Deterrents to immunization of these groups include lack of awareness of the risk of disease and its consequences, lack of effective public or private sector programs, and vaccine cost. Difficulty in gaining access to these populations is also a problem. Further, there has been limited success in providing vaccine to persons in high-risk groups due to rapid acquisition of infection after beginning high-risk behaviors, low initial vaccine acceptance, and low completion rates.

A comprehensive strategy to eliminate hepatitis B virus transmission was recommended in 1991, and includes (a) prenatal testing of pregnant women for HBsAg to identify newborns who require immunoprophylaxis for the prevention of perinatal infection and to identify household contacts who should be vaccinated, (b) routine vaccination of infants, (c) vaccination of adolescents, and (d) vaccination of adults at high risk of infection.

HEPATITIS B VACCINE

Characteristics

A **plasma-derived vaccine** was licensed in the United States in 1981. It was produced from 22nm HBsAg particles purified from the plasma of human carriers. The vaccine was safe and effective, but was not well accepted, possibly because of unbased fears of transmission of live HBV and other blood-borne pathogens (e.g., human immunodeficiency virus). This vaccine was removed from the U.S. market in 1992.

Recombinant hepatitis B vaccine was licensed in the United States in July 1986, and was the first vaccine licensed in the United States produced by recombinant DNA technology. A second, similar vaccine was licensed in August 1989.

Recombinant vaccine is produced by inserting a plasmid containing the gene for HBsAg into common baker's yeast (Saccharomyces cerevisiae). Yeast cells then produce HBsAg, which is harvested and purified. The recombinant vaccine contains over 95% HBsAg protein (5 to 40 mcg/ml); yeast-derived proteins may constitute up to 5% of the final product, but no yeast DNA

is detectable in the vaccine. HBV infection cannot result from use of the recombinant vaccine, since no potentially infectious viral DNA or complete viral particles are produced in the recombinant system. Vaccine HBsAg is adsorbed to aluminum hydroxide.

Hepatitis B vaccine is produced by two manufacturers in the United States - Merck and Company Vaccine Division (Recombivax HB®) and Glaxo SmithKline Pharmaceuticals (Engerix-B®). Both vaccines are available in both pediatric and adult formulations. Although the antigen content of the vaccines differ (see table below and in Appendix A), vaccines made by different manufacturers are interchangeable, except for the 2-dose schedule for adolescents aged 11-15 years. Only Merck vaccine is approved for this schedule. Providers must always follow the manufacturer's dosage recommendations.

Both the pediatric and adult formulations of Recombivax HB are approved for use in any age group. For example, the adult formulation of Recombivax HB may be used in children (0.5 ml) and adolescents (0.5 ml). However, pediatric Engerix-B is approved for use only in children and adolescents <20 years of age. The adult formulation of Engerix-B is not approved for use in infants and children, but may be used in both adolescents (11-19 years of age) and adults (see table below and in Appendix A).

Immunogenicity and Vaccine Efficacy

After three intramuscular doses of hepatitis B vaccine, over 90% of healthy adults and over 95% of infants, children, and adolescents (from birth to 19 years of age) develop adequate antibody responses. However, there is an age-specific decline in immunogenicity. After age 40 years, approximately 90% of recipients respond to a 3-dose series, and by 60 years, only 75% of vaccinees develop protective antibody titiers.

The vaccine is 80% to 100% effective in preventing infection or clinical hepatitis in those who receive the complete course of vaccine. Larger vaccine doses (2 to 4 times the normal adult dose) or an increased number of doses are required to induce protective antibody in a high proportion of hemodialysis patients and may also be necessary in other immunocompromised persons.

Recommended Dose of Hepatitis B Vaccine

Group	Vaccine	
	Recombivax HB* Dose (ml)	Engerix-B* Dose (ml)
Infants† and children <11 years of age	5µg (0.5)	10µg (0.5)
Adolescents 11-19 years	5µg (0.5)	10µg (0.5)
Adults ≥20 years	10µg (1.0)	20µg (1.0)
Dialysis patients and other compromised persons	40µg§ (1.0)	40µg¶ (2.0)

* Usual schedule: Three doses at 0, 1, 6 months.
† Infants whose mothers are HBsAg positive should also receive hepatitis B immune globulin (HBIG) at birth.
§ Special formulation for dialysis patients.
¶ Two 1.0 ml doses given at one site in a four-dose schedule at 0, 1, 2, and 6 months.

The recommended dosage of vaccine differs depending on the age of the recipient and type of vaccine (see table). Hemodialysis patients should receive a 40 mcg dose in a series of three or four doses. Recombivax HB has a special dialysis patient formulation that contains 40 mcg/ml. The deltoid muscle is the recommended site for hepatitis B vaccination in adults and children, while the anterolateral thigh is recommended for infants and neonates. Immunogenicity of vaccine in adults is lower when injections are given in the buttock.

Available data show that vaccine-induced antibody levels decline with time. Nevertheless, immune memory remains intact for >15 years following immunization, and both adults and children with declining antibody levels are still protected against significant HBV infection (i.e., clinical disease, HBsAg antigenemia, or significant elevation of liver enzymes). Exposure to HBV results in an anamnestic anti-HBs response that prevents clinically significant HBV infection. Chronic HBV infection has only rarely been documented among vaccine responders.

For adults and children with normal immune status, booster doses of vaccine are not recommended, nor is routine serologic testing to assess immune status of vaccinees indicated. The need for booster doses after longer intervals will continue to be assessed as additional information becomes available.

For hemodialysis patients, the need for booster doses should be assessed by annual testing of vaccinees for antibody levels, and booster doses should be provided when antibody levels decline below 10 mIU/ml.

VACCINATION SCHEDULE AND USE

Infants and Children

Hepatitis B vaccination is recommended for all infants soon after birth and before hospital

discharge. Infants and children <11 years of age should receive 0.5 ml (5 mcg) of pediatric or adult formulation Recombivax HB (Merck) or 0.5 ml (10 mcg) of pediatric Engerix-B (Glaxo SmithKline). Primary vaccination consists of three intramuscular doses of vaccine with the second and third doses given 1 to 4 and 2 to 17 months, respectively, after the first. The first dose may be administered by age 2 months if the infant's mother is HBsAg-negative.

Because the highest titers of anti-HBs are achieved when the last two doses of vaccine are spaced at least 4 months apart, schedules that achieve this spacing are preferable. However, schedules with 2-month intervals between doses, which conform to schedules for other childhood vaccines, have been shown to produce good antibody responses and may be appropriate in populations in which it is difficult to ensure that infants will be brought back for all their vaccinations. How-ever, the third dose must be administered at least 2 months after the second dose, and should follow the first dose by at least 4 months. **For infants, the third dose should not be given prior to 6 months of age**. It is not necessary to add doses or restart the series if the interval between doses is longer than recommended.

Premature infants born to HBsAg-positive women and women with unknown HBsAg status should receive immunoprophylaxis with hepatitis B vaccine and hepatitis B immune globulin (HBIG) beginning at or shortly after birth (see details below). For premature infants of HBsAg-negative mothers, the optimal timing of hepatitis B vaccination has not been determined. Some studies suggest that decreased seroconversion rates might occur in some premature infants with low birthweights (i.e., <2000 grams) following administration of hepatitis B vaccine at birth. However, by chronological age 1 month, all premature infants, regardless of initial birth weight or gestational age are as likely to respond as adequately as older and larger children. Low birthweight infants of HBsAg-negative mothers can receive the first dose of the hepatitis B vaccine series at chronological age 1 month. Premature infants discharged from the hospital before chronologicdal age 1 month can also be administered hepatitis B vaccine at discharge, if they are medically stable and have gained weight consistently. The full recommended dose should be used. Divided or reduced doses are not recommended.

Hepatitis B vaccine is also available in combination with *Haemophilus influenzae* type B (Hib) vaccine (COMVAX®, Merck). Each dose of COMVAX contains 7.5 micrograms of PRP-OMP Hib vaccine (PedvaxHIB®), and 5 micrograms of hepatitis B surface antigen. The dose of hepatitis B surface antigen is the same as that contained in Merck's pediatric formulation. The immunogenicity of the combination vaccine is equivalent to that of the individual antigens administered at separate sites. Adverse reactions following the combination vaccine are uncommon, as they are following vaccination with the individual antigens.

COMVAX is licensed for use at 2, 4, and 12-15 months of age. It may be used whenever either antigen is indicated and the other antigen is not contraindicated. However, the vaccine **must not be administered to infants younger than 6 weeks of age** because of potential suppression of the immune response to the Hib component (see Hib chapter for more details). COMVAX **must not be used for doses at birth or one month of age** for a child on a 0-1-6 month hepatitis B vaccine schedule.

Adolescents

Routine hepatitis B vaccination is recommended for all children and adolescents through age 18 years. **All children not previously vaccinated with hepatitis B vaccine should be vaccinated at 11-12 years of age** with the age-appropriate dose of vaccine. When adolescent vaccination programs are being considered, local data should be considered to determine the ideal age group to vaccinate (i.e., preadolescents, young adolescents), to achieve the highest vaccination rates. The vaccination schedule should be flexible and take into account the feasibility of delivering three doses of vaccine to this age group. Unvaccinated older adolescents should be vaccinated whenever possible. Those in groups at risk for HBV infection (e.g., Asian and Pacific Islanders, sexually active) should be identified and vaccinated in settings serving this age group (i.e., schools, sexually transmitted disease clinics, detention facilities, drug treatment centers).

Adolescents 11-19 years of age should receive 0.5 ml (5 mcg) of pediatric or adult formulation Recombivax HB (Merck) or 0.5 ml (10 mcg) of pediatric formulation Engerix-B (Glaxo SmithKline). The adult formulation of Engerix-B may be used in adolescents, but the approved dose is 1.0 ml (20 mcg).

The usual schedule for adolescents is two doses separated by no less than 4 weeks, and a third dose 4-6 months after the second dose. If an **accelerated schedule** is needed, the minimum interval between the first two doses is 4 weeks, and the minimum interval between the second and third doses is 8 weeks. However, **the first and third doses should be separated by no less than 4 months**. Doses given at less than these minimum intervals should not be counted as part of the vaccination series.

In 1999, the Food and Drug Administration approved an alternative hepatitis B vaccination schedule for adolescents 11-15 years of age. This alternative schedule is for two 10 mcg doses of RecombivaxHB separated by 4-6 months. Seroconversion rates and postvaccination anti-HBs antibody titers were similar using this schedule and the standard schedule of three 5 mcg doses of RecombivaxHB. This alternative schedule is only approved for children 11-15 years of age, and for Merck's hepatitis B vaccine. The 2-dose schedule should be completed by age 16 years.

Adults

Routine preexposure vaccination should be considered for groups of adults who are at increased risk of HBV infection. Adults 20 years of age and older should receive 1.0 ml (10 mcg) of pediatric or adult formulation Recombivax HB (Merck) or 1.0 ml (20 mcg) of adult formulation Engerix-B (Glaxo SmithKline). The pediatric formulation of Engerix-B is not approved for use in adults.

The usual schedule for adults is two doses separated by no less than 4 weeks, and a third dose 4-6 months after the second dose. If an **accelerated schedule** is needed, the minimum interval between the first two doses is 4 weeks, and the minimum interval between the second and third

doses is 8 weeks. However, the **first and third doses should be separated by no less than 4 months**. Doses given at less than these minimum intervals should not be counted as part of the vaccination series.

Adults who are at increased risk of HBV infection from sexual transmission include **men who have sex with other men, heterosexuals with multiple sexual partners, persons diagnosed with a recently acquired sexually transmitted disease, and prostitutes**.

Injection drug users who share needles are at extremely high-risk for HBV infection. All injection drug users who are susceptible to HBV should be vaccinated as soon as possible after their drug use begins.

Long-term male prison inmates are at increased risk of HBV infection because of injection drug use, homosexual activity, or other factors. The prison setting provides an access point for vaccination of inmates with histories of high-risk behavior.

Persons on hemodialysis are at increased risk of HBV infection because of contact with large amounts of blood. Although the hepatitis B vaccine is less effective in these patients, it is recommended for all susceptible hemodialysis patients.

The risk of **health care workers** contracting HBV infection depends on how often they are exposed to blood or blood products through percutaneous and permucosal exposures. Any health care or public safety worker may be at risk for HBV exposure, depending on the tasks performed. If those tasks involve contact with blood or blood-contaminated body fluids, then such workers should be vaccinated. Risk is often highest during training periods. Therefore, it is recommended that vaccination be completed during training in schools of medicine, dentistry, nursing, laboratory technology, and other allied health professions.

Other Groups Who May be Candidates for Hepatitis B Vaccine

The special behavioral and medical problems encountered in **institutions for the developmentally disabled** make this a high-risk setting, and clients and staff should be vaccinated. The risk of HBV infection in these institutions is related to contact with blood and also with bites and contact with skin lesions and other body fluids that contain HBV. Clients and staff of group and foster homes where a carrier is known to be present should also be vaccinated.

In certain U.S. populations, such as **Alaskan Natives, Pacific Islanders, and immigrants and refugees from HBV endemic areas**, HBV infection is highly endemic and transmission occurs primarily during childhood. In such groups, vaccination of all infants is particularly important. Immigrants and refugees from areas with highly endemic HBV disease should be screened for HBV upon resettlement in the U.S. If a carrier is identified, all susceptible household members should be vaccinated. Even if no carriers are found, vaccination is recommended for susceptible children less than 7 years of age because of the high rate of interfamilial spread of HBV.

Adoptees, orphans and unaccompanied minors from countries of high or intermediate HBV endemicity should be screened for HBsAg, and, if positive, their household members should be vaccinated.

Household members and sexual partners of HBV carriers should be tested and, if susceptible, should be vaccinated.

Adults and children who plan to travel to areas outside the United States that have high rates of HBV infection should be vaccinated if they plan to stay in these areas for more than 6 months and have close contact with the local population. Persons traveling for shorter durations who may have sexual contact with local persons in areas where HBV infection is common should also be vaccinated. Persons traveling abroad who will perform medical procedures in areas where HBV infection is common are at very high risk.

Recipients of certain blood products, such as those with hemophilia, are at high risk of infection. Vaccination should be initiated at the time their specific clotting disorder is identified.

Persons who have casual contact with carriers at schools and offices are at little risk of HBV infection from such contact, and vaccine is not recommended for them. Unless special circumstances exist, such as behavior problems (biting or scratching) or medical conditions (severe skin disease) that might facilitate transmission, vaccination of contacts of carriers in child care centers is not indicated. However, routine vaccination of all persons <18 years of age is recommended.

SEROLOGIC TESTING OF VACCINE RECIPIENTS

Prevaccination Serologic Testing

The decision to screen potential vaccine recipients for prior infection depends on the cost of vaccination, the cost of testing for susceptibility, and the expected prevalence of immune persons in the group. Screening is usually cost-effective, and should be considered, in groups with a high risk of HBV infection (HBV markers prevalence >20%) such as male homosexuals, injection drug users, Alaskan natives, Pacific Islanders, children of immigrants from endemic countries, and family members of HBsAg carriers. Screening is usually not cost-effective for groups with a low expected prevalence of HBV serologic markers such as health professionals in their training years.

Serologic testing is not recommended before routine vaccination of infants and children.

Post-vaccination Serologic Testing

Testing for immunity following vaccination is not recommended routinely, but should be considered for persons whose subsequent management depends on knowing their immune status, such as dialysis patients and staff, and persons in whom a suboptimal response may be

anticipated, such as those who have received vaccine in the buttock. When necessary, post-vaccination testing should be done between 1-2 months after completion of the vaccine series to provide definitive information on response to the vaccine.

All infants born to HBsAg-positive women should be tested 3-9 months after their third dose of hepatitis B vaccine (i.e., at 9-15 months of age). If HBsAg is not present and anti-HBs antibody is present, children can be considered to be protected.

In 1997, ACIP and the Hospital Infection Control Practices Advisory Committee published comprehensive recommendations for the immunization of health care workers. One of the recommendations was that **health care workers who have contact with patients or blood and are at ongoing risk for injuries with sharp instruments or needlesticks should be routinely tested for antibody after vaccination**. However, a catch-up program of serologic testing for health care providers vaccinated prior to December 1997 is not recommended. These individuals should be tested as necessary if they have a significant exposure to HBV (see postexposure prophylaxis section below).

Routine postvaccination testing is not recommended for persons at low risk of exposure, such as public safety workers and health care workers without direct patient contact.

Vaccine Nonresponse

A number of factors have been associated with nonresponse to hepatitis B vaccine. These include vaccine factors (e.g., dose, schedule, injection site), and host factors. Older age (>40 years), male gender, obesity, smoking, and chronic illness have been independently associated with nonresponse to hepatitis B vaccine. Further vaccination of nonresponders to a primary vaccination series administered in the deltoid muscle produces adequate response in 15% to 25% after one additional dose and in 30% to 50% after three additional doses.

Persons who do not respond to the first series of hepatitis B vaccine should complete a second three-dose vaccine series. The second vaccine series should be given on the usual 0, 1, 6- month schedule. A 0, 1, 4-month accelerated schedule may also be used. Revaccinated health care workers and others for whom postvaccination serologic testing is recommended should be retested at the completion of the second vaccine series.

Fewer than 5% of persons receiving 6 doses of hepatitis B vaccine administered by the appropriate schedule in the deltoid muscle fail to develop detectable anti-HBs antibody. Some persons who are anti-HBs negative following 6 doses may have a low level of antibody that is not detected by routine serologic testing. One reason for persistent nonresponse to hepatitis B vaccine is that the person is chronically infected with HBV. Persons who fail to develop detectable anti-HBs after 6 doses should be tested for HBsAg. Persons who are found to be HBsAg-positive should be counseled accordingly. Vaccine nonresponders who are HBsAg-negative should be considered susceptible to HBV infection and should be counseled regarding precautions to prevent HBV infection and the need to obtain HBIG prophylaxis for

any known or probable parenteral exposure to HBsAg-positive blood (see postexposure prophylaxis table below).

POST-EXPOSURE MANAGEMENT

Hepatitis B vaccine is recommended as part of the therapy used to prevent hepatitis B infection following exposure to HBV. Depending on the exposure circumstance the hepatitis B vaccine series may be started at the same time as other therapy, primarily treatment with hepatitis B immune globulin (HBIG).

Infants born to women who are HBsAg-positive (i.e., acutely or chronically infected with HBV) are at extremely high risk of HBV transmission and chronic HBV infection. Hepatitis B vaccination and one dose of HBIG administered within 24 hours after birth are 85%-95% effective in preventing both HBV infection and chronic infection. Hepatitis B vaccine administered alone beginning within 24 hours after birth is 70%-95% effective in preventing perinatal HBV infection.

HBIG (0.5 ml) should be given IM, preferably within 12 hours of birth. Hepatitis B vaccine should be given IM in three doses. The first dose should be given at the same time as HBIG, but at a different site. If vaccine is not immediately available, the first injection should be given within 7 days of birth. The second and third doses should be given 1-2 months and 6 months, respectively, after the first. Testing for HBsAg and anti-HBs is recommended at 9 to 15 months of age (3 to 9 months after the third dose) to monitor the success of therapy. If the mother's HBsAg status is not known at the time of birth, the infant should be vaccinated within 12 hours of birth.

HBIG given at birth does not interfere with the administration of other vaccines administered at 2 months of age. Subsequent doses of hepatitis B vaccine do not interfere with the routine pediatric vaccine schedule.

Infants born to HBsAg-positive women who weigh less than 2 kilograms at birth should be given postexposure prophylaxis as described above. However, the initial vaccine dose (at birth) should not be counted in the required 3-dose schedule. The next dose in the series should be administered as described for low birthweight infants, when the infant is chronologic age 1 month. The third dose should be given 1-2 months after the second, and the fourth dose should be given at 6 months of age. These infants should be tested for HBsAg and anti-HBs at 9-15 months of age.

Women admitted for delivery whose HBsAg status is unknown should have blood drawn for testing. While test results are pending the infant should receive the first dose of hepatitis B vaccine without HBIG within 12 hours of birth. If the mother is found to be HBsAg positive, the infant should receive HBIG as soon as possible but not later than 7 days of age. If the infant does not receive HBIG it is important that the second dose of vaccine be administered at 1-2 months of age.

Premature infants (<2000 grams birth weight) whose mother's HBsAg status is unknown should receive hepatitis B vaccine and HBIG within 12 hours of birth, unless results of HBsAg testing can be available in <12 hours. As described above, the vaccine dose administered at birth should not be counted as part of the series, and the infant should receive 3 additional doses beginning at age 1 month. The vaccine series should be completed by 6 months of age.

There are few data available on the use of COMVAX in infants born to women who have acute or chronic infection with hepatitis B virus (i.e., HbsAg-positive). COMVAX is not currently licensed for infants whose mothers are known to be acutely or chronically infected with HBV. **COMVAX should never be used in infants <6 weeks of age**. COMVAX may be administered at the same time as other childhood vaccines given at >6 weeks of age.

After a percutaneous (needle stick, laceration, bite) or permucosal exposure that contains or might contain HBV, blood should be obtained from the person who was the source of the exposure to determine their HBsAg status. Management of the exposed person depends on the HBsAg status of the source, and the vaccination and anti-HBs response status of the exposed person. Recommended postexposure prophylaxis is described on the table below.

Recommended Postexposure Prophylaxis for Percutaneous or Permucosal Exposure to Hepatitis B Virus

Vaccination and antibody status of exposed person		Treatment when source is		
		HBsAg* Positive	HBsAg Negative	Not tested or infection status unknown
Unvaccinated		HBIG† X 1; Initiate hepatitis B series	Initiate hepatitis B series	Initiate hepatitis B vaccine series
Previously Vaccinated	**Known Responder§**	No treatment	No treatment	No treatment
	Known non-responder, no revaccination	HBIG X 1 and initiate revaccination	No treatment; consider revaccination for future protection	If known high-risk source, treat as if source were HBsAg positive
	Known non-responder to initial & revaccination series	HBIG X 2 – second dose one month after the first	No treatment	If known high-risk source, treat as if source were HBsAg positive
	Antibody response unknown	Test exposed person for anti-HBs¶ - If adequate‡, no treatment - If inadequate‡, HBIG X 1 and initiate revaccination, evaluate antibody response at 6 months	No testing, no treatment	Test exposed person for anti-HBs¶ - If adequate‡, no treatment - If inadequate‡, initiate revaccination, evaluate antibody response at 6 months

* Hepatitis B surface antigen
† Hepatitis B immune globulin (HBIG) dose 0.06 mL/kg administered intramuscularly
§ Responder is a person with anti-HBs antibody level of ≥10 mIU/mL
¶ Antibody to hepatitis B surface antigen
‡ Adequate response is anti-HBs ≥10 mIU/mL; inadequate response is anti-HBs <10 mIU/mL

Susceptible Sexual Partners of Persons with Acute HBV Infection, or Hepatitis B Carriers

For susceptible sexual contacts of persons with acute HBV infection a single dose of HBIG (0.06ml/kg) given within 14 days of the last sexual contact is recommended. If the last sexual contact is >14 days, hepatitis B vaccination should be initiated, although the amount of protection afforded by postexposure prophylaxis given this late is not known. For sexual partners of persons with chronic HBV infection, postexposure prophylaxis with hepatitis B vaccine alone is recommended. HBIG is not recommended in this situation. Postvaccination anti-HBs testing should be considered for sexual partners of persons with chronic HBV infection.

Household Contacts of Persons with Acute HBV Infection

Infants have close contact with the mother or primary care giver, and are at increased risk of chronic HBV infection. An unvaccinated infant whose mother or primary care giver has acute HBV infection should receive HBIG (0.5 ml) along with the first dose of the hepatitis B vaccine series. HBIG is not needed for infants who have received two doses of vaccine or are scheduled to receive the second dose of vaccine. The second vaccine dose should be given and/or vaccination should be completed on schedule. Household contacts of persons with acute HBV infection who have had a blood exposure to the infected person (e.g., sharing a toothbrush or razor) should receive HBIG and begin the vaccine series. Routine hepatitis B vaccination should be considered for nonsexual household contacts of the infected person who do not have a blood exposure, especially for children and adolescents.

Combination Hepatitis A and Hepatitis B Vaccine

In May 2001, the Food and Drug Administration approved a combination hepatitis A and hepatitis B vaccine (Twinrix®, Glaxo SmithKline). Each dose of Twinrix contains 720 EL.U. of hepatitis A vaccine (equivalent to a pediatric dose of Havrix®), and 20 mcg of hepatitis B surface antigen protein (equivalent to an adult dose of Engerix-B®). The vaccine is administered in a 3-dose series at 0, 1, and 6 months. Appropriate spacing of the doses must be maintained to assure long term protection from both vaccines. The first and third doses of Twinrix should be separated by at least 6 months. The first and second doses should be separated by at least 4 weeks, and the second and third doses should be separated by at least 8 weeks, as in the hepatitis B schedule. It is not necessary to restart the series or add doses if the interval between doses is longer than the recommended interval.

Twinrix is approved for persons aged 18 years and older, and can be used in persons in this age group with indications for both hepatitis A and hepatitis B vaccines. Because the hepatitis B component of Twinrix is equivalent to a standard dose of hepatitis B vaccine, the schedule is the same whether Twinrix or single-antigen hepatitis B vaccine is used. See the hepatitis A chapter for information on schedules that include both Twinrix and single-antigen hepatitis A vaccine.

ADVERSE REACTIONS FOLLOWING VACCINATION

The most common adverse reaction following hepatitis B vaccine is **pain at the site of injection**, reported in 13% to 29% of adults and 3% to 9% of children. **Mild systemic complaints**, such as fatigue, headache, and irritability have been reported in 11% to 17% of adults and 0% to 20% of children. Low-grade fever (>37.7^{O}C) has been reported in 1% of adults and 0.4% to 6.4% of children. Serious systemic adverse events and allergic reactions are rarely reported following hepatitis B vaccine.

There is no evidence that administration of hepatitis B vaccine at or shortly after birth increases the number of febrile episodes, sepsis evaluations or allergic or neurologic events in the newborn period.

Hepatitis B vaccine has been alleged (mostly in the media) to cause or exacerbate multiple sclerosis. However, recent large population-based studies have shown there is no association between receipt of hepatitis B vaccine and either the development of multiple sclerosis or exacerbation of the course of multiple sclerosis is persons already diagnosed with the disease.

CONTRAINDICATIONS AND PRECAUTIONS TO VACCINATION

A serious allergic reaction to a prior dose of hepatitis B vaccine or a vaccine component is a contraindication to further doses of vaccine. Such allergic reactions are rare.

Persons with **moderate to severe acute illness** should not be vaccinated until their conditions improve. However, minor illnesses, such as upper respiratory infections, are not a contraindication to vaccination.

No information is available about the safety of the vaccine in pregnant women. However, because the vaccine contains only particles that do not cause HBV infection, there should be no risk. In contrast, if a pregnant woman acquires HBV infection, it may cause severe disease in the mother and chronic infection in the newborn baby. Therefore, pregnant women who are otherwise eligible can be given hepatitis B vaccine.

Hepatitis B vaccine does not contain live virus, so it may be used in persons with immuno-deficiency. However, response to vaccination in such persons may be suboptimal.

VACCINE STORAGE AND HANDLING

Hepatitis B vaccines should be stored refrigerated at 2^{O}-8^{O}C (35^{O}-46^{O}F), but not frozen. Freezing destroys the potency of the vaccine.

HEPATITIS B IMMUNE GLOBULIN

Hepatitis B immune globulin (HBIG) is prepared by cold ethanol fraction of plasma from

selected donors with high anti-HBs titers; contains an anti-HBs titer of at least 1:100,000, by RIA. It is used for passive immunization for (1) accidental (percutaneous, mucous membrane) exposure, (2) sexual exposure to HBsAg-positive person, (3) perinatal exposure of infant, or (4) household exposure of an infant less than 12 months old to a primary caregiver with acute hepatitis B.

All candidates for HBIG are, by definition, in a high-risk category, and should therefore be considered for vaccine as well.

Immune globulin (IG) is prepared by cold ethanol fractionation of pooled plasma and contains low titers of anti-HBs. Because titers are relatively low, IG has no valid current use for HBV disease, unless hepatitis B immune globulin is unavailable.

MATERNAL SCREENING

In 1988, the Advisory Committee on Immunization Practices (ACIP), in consultation with the American College of Obstetrics and Gynecology and the American Academy of Pediatrics, recommended that all pregnant women should be routinely tested for HBsAg during an early prenatal visit, in each pregnancy. If a woman has not been screened prenatally, or the results are unavailable at the time of delivery, HBsAg testing should be done at admission for delivery. This identifies infants born to HBsAg positive mothers for prompt prophylaxis at birth, as well as at 1 and 6 month follow-ups. Also, household members and sexual partners of HBV carriers should be evaluated for the need for hepatitis B vaccine.

SELECTED REFERENCES

Ascherio A, Zhang SM, Hernan MA, et al. Hepatitis B vaccination and the risk of multiple sclerosis. *N Engl J Med* 2001;344:327-32.

CDC. Hepatitis B virus: a comprehensive strategy for eliminating transmission in the United States through universal childhood vaccination. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 1991;40(RR-13):1-25. (currently being revised)

CDC. Immunization of health-care workers. Recommendations of the Advisory Committee on Immunization Practices (ACIP) and the Hospital Infection Control Practices Advisory Committee (HICPAC). *MMWR* 1997;46(RR-18):1-42.

CDC. Updated U.S. Public Health Service guidelines for the management of occupational exposures to HBV, HCV, and HIV and recommendations for postexposure prophylaxis. *MMWR* 2001;50(RR-11):1-42..

Confavreux C, Suissa S, Saddier P, et al. Vaccinations and the risk of relapse in multiple sclerosis. *N Engl J Med* 2001;344:319-26.

Evans AS, Kaslow RA, eds. *Viral Infections of Humans. Epidemiology and Control.* 4th edition. New York, NY: Plenum Medical Book Company, 1997.

Lee WM. Hepatitis B virus infection. *N Engl J Med* 1997;337:1733-45.

Lewis E, Shinefield HR, Woodruff BA, et al. Safety of neonatal hepatitis B vaccine administration. *Pediatr Infect Dis J* 2001;20:1049-54.

Pickering L, ed. *2000 Red Book: Report of the Committee on Infectious Diseases*. 25th ed. Elk Grove Village, IL: American Academy of Pediatrics, 2000.

Plotkin SA, Orenstein WA, eds. *Vaccines*. 3rd edition. Philadelphia: W.B. Saunders Company, 1999.